Remarks/Arguments

A. Status of the Claims

Claims 1-12 and 14-17 were pending at the time the Action was mailed. Claim 1 has been amended, as described herein. Support for this amendment can be found in the specification and claims as originally filed, *e.g.*, page 4, line 23 to page 5, line 2; page 5, lines 18-20; page 6, lines 1-6; Example 1 (page 12, line 27 to page 15, line 15); and originally-filed claim 16. Claims 5 and 9 have been amended to reflect proper dependencies. Claim 11 has been amended for clarity purposes to reflect amendments made to claim 1. Claims 2-4, 6-8 and 17 have been canceled without prejudice or disclaimer. Claim 25 is new. Support for claim 25 may be found in the specification as originally filed. *See, e.g.*, page 4, line 23 to page 5, line 2; and Example 1 (page 12, line 27 to page 15, line 15).

Claims 1, 5, 9, 11-12, 14-16 and 25 are pending.

B. The Indefiniteness Rejection Is Overcome

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, for allegedly to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Action contends that claim 2 fails to further limit independent claim 1.

Applicant disagrees. However, in an effort to further prosecution and secure prompt allowance in this case, claim 2 is canceled without prejudice or disclaimer. The rejection is therefore moot, and Applicant respectfully requests that it be withdrawn.

C. The Obviousness Rejections Are Overcome

1. The Rejection of Claims 1-7, 10-12 and 14-17 Is Overcome

Claims 1-7, 10-12 and 14-17 are rejected under 35 U.S.C. § 103(a) as being obvious over Gervais (U.S. Patent No. 6,340,695) in view of Apfel *et al.* (*Anesthesiology*, 91:693-700 (1991)) ("Apfel").

Applicant disagrees with this rejection. The claims, prior to any amendment, were not rendered obvious by the cited references. However, in an effort to further the prosecution and secure prompt allowance in this case, claim 1 has been amended without prejudice or disclaimer to recite the following:

> 1. A method of reducing post-surgical vomiting in a patient 6-24 hours post-surgery comprising:
>
> (a) orally administering to the patient at least a first delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients the evening prior to surgery, and
>
> (b) orally administering to the patient a second delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients 0-6 hours after surgery.

Amended claim 1 thus incorporates at least the subject matter of original claim 8 (now canceled), which was not part of the present rejection—namely, wherein Doxylamine Succinate and Pyridoxine Hydrochloride are orally administered in a delayed release formulation.

For at least this reason, Applicant respectfully requests that this rejection be withdrawn. The following arguments will more specifically address the obviousness rejection regarding now-canceled claim 8.

2. The Rejection of Claims 8 and 9 Is Overcome

Claims 8 and 9 are rejected under 35 U.S.C. § 103(a) as being obvious over Gervais in view of Apfel as applied to claims 1-7, 10-12 and 14-17, and further in view of Ansel *et al.* (Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippencott Williams and Wilkins, Chapter 8, p 229 (1999)) ("Ansel").

Applicant disagrees. The claims, prior to any amendment made above, were not rendered obvious by the cited references. However, in an effort to further the prosecution and secure prompt allowance in this case, claim 1 has been amended as noted above. Claim 1 is not rendered obvious by the cited references or by the common knowledge in the art, as will be

discussed below. Moreover, dependent claims 5, 9, 11-12 and 14-16 are also not obvious. *See* MPEP § 2143.03 ("If an independent claim is unobvious under 35 U.S.C. § 103, then any claim dependent there from is nonobvious.")

a. There is no factual basis to support the obviousness rejection

As noted in the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*, 72 Fed. Reg. 57526, 57527 (MPEP § 2141) ("Guidelines"), "When making an obviousness rejection, Office personnel must... ensure that the written record includes findings of fact concerning ***the state of the art*** and the teachings of the references applied." The Guidelines further emphasize the importance of factual findings by stating, "Factual findings made by Office personnel are the necessary underpinnings to establish obviousness." *Id.* However, a factual assessment of the state of the art relevant to the claimed invention does not appear to be addressed by the present Action. Indeed, the obviousness rejection cannot stand in view such an analysis.

The content of claim 1 provides the context for analyzing the scope and content of the prior art. Claim 1 recites, in part, "A method of reducing post-surgical vomiting in a patient comprising: (a) orally administering to the patient... [a first or second] delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride...." At a minimum, the state of the art did not contemplate oral administration of a delayed release formulation comprising Doxylamine Succinate and Pyridoxine Hydrochloride to reduce post-surgical vomiting at the time the application was filed.

i. State of the art regarding oral administration of a delayed release formulation comprising Doxylamine Succinate and Pyridoxine Hydrochloride

Existing antiemetics used for preventing or treating post-operative nausea and vomiting (PONV) are generally administered in one of two ways: intravenously, or orally with immediate

release. These methods of administration allow the active ingredients to be released and available as soon as possible in the patients. Nothing in the state of the art at the time the application was filed suggested use of a delayed release formulation to address the problem of post-operative vomiting. This is because in this field, the desired effects are usually wanted immediately after administration of an antiemetic medicine.

For example, the enclosed article entitled, "Managing Nausea and Vomiting," dated February 2003 and written namely for critical care nurses, summarizes the antiemetic therapy that was then recommended by the American Society of Health System Pharmacists, the American Society of Clinical Oncology, and the Mayo Clinic Clinical Practice Guidelines. *See e.g.*, Appendix 1, Table 1 on pages 34-37. In this table, intravenous (IV) administration of an antiemetic agent for PONV prevention is recommended to be done at a maximum of 15-30 minutes before induction of anesthesia and up through intraoperative administration, and oral administration is recommended to be done at a maximum of one hour before induction of anesthesia. None of the recommended agents comprise Doxylamine Succinate or Pyridoxine Hydrochloride as active ingredients. This document contains no recommendation, suggestion, or practice tending to use a delayed release formulation, a formulation comprising Doxylamine Succinate and Pyridoxine Hydrochloride, or even less a delayed release formulation comprising these active ingredients.

ii. State of the art regarding a formulation comprising Doxylamine Succinate and Pyridoxine Hydrochloride to reduce post-surgical vomiting

Although a formulation comprising Doxylamine Succinate and Pyridoxine Hydrochloride (*e.g.*, Diclectin®) has been proven efficient in the treatment of nausea and vomiting during pregnancy, the state of the art at the time the application was filed did not contemplate its use for reducing the occurrence of post-operative vomiting. This is confirmed by the enclosed article by

Dr. Brenda Reeve *et al.*, published in the *Canadian Journal of Anesthesia* in 2005 (Appendix 2): "Diclectin® (DCL) is an effective antiemetic used for relief of nausea and vomiting in pregnancy. It is unknown whether DCL is effective in the prevention of postoperative nausea and vomiting (PONV)." *Can. J. Anesth.*, 52:55-61 (2005), at Abstract. These statements regarding the state of the art counsel against a finding of obviousness.

In view of the status of the state of the art at the time the application was filed, there is no support for a finding of obviousness regarding the present claims. For at least this reason, Applicant respectfully requests that the obviousness rejection be withdrawn.

b. The Cited References Fail To Teach or Suggest The Claimed Invention

The recent *KSR v. Teleflex* Supreme Court decision did not change the requirement that to support an obviousness rejection, a reference, alone or in combination, must teach or suggest every element of a claimed invention. MPEP § 2143. In the present case, the cited references fail to teach, "A method of reducing post-surgical vomiting in a patient 6-24 hours post-surgery comprising: (a) orally administering to the patient at least a first delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients the evening prior to surgery, and (b) orally administering to the patient a second delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients 0-6 hours after surgery." As such, the obviousness rejection cannot stand.

i. Gervais

Gervais generally teaches a rapid onset formulation comprising Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients and having specific *in-vitro* dissolution profiles, such formulation being useful in the treatment of nausea and vomiting. *See, e.g.*, Gervais, Abstract and col. 2, lines 27-40. As noted by the Action at page 4, Gervais recites that

"the formulation [...] may be used in the human and veterinary fields of medicine whenever ***symptoms*** of nausea and/or vomiting require medical intervention." Gervais, column 2, lines 56-59 (emphasis added). Thus, as noted in Applicant's Request for Continued Examination filed July 6, 2007, the formulation of Gervais comprising Doxylamine Succinate and Pyridoxine Hydrochloride is used after some nausea and/or vomiting symptoms are present and require medical intervention, *i.e.*, on existing symptoms. Importantly, Gervais does not teach or suggest "orally administering to the patient at least a first delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients the evening prior to surgery," nor "orally administering to the patient a second delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients 0-6 hours after surgery" as recited in claim 1. Aspects of these facts are conceded by the Action. *See* Action at page 6 (explaining that Gervais "does not specifically teach 'reducing post-surgical vomiting'...comprising the administration before, during[,] after (at regular intervals), before anesthesia, on an outpatient basis, on an evening prior to, a morning of the day of and after surgery...."). Thus, Gervais does not teach or suggest the claimed invention.

ii. Apfel

Apfel discloses a risk score for predicting postoperative nausea and vomiting based on, for example, four main risk factors, namely female gender, prior history of motion sickness or post-operative nausea or vomiting, nonsmoking, and the use of postoperative opioids. *See, e.g.*, Apfel, Abstract. Apfel concludes, for example, that "a modification or change of the anesthetic technique might be considered if two or more risk factors are present." *Id.*, page 699, col. 2. According to his proposed risk score, one method could entail using a prophylactic antiemetic treatment in "high-risk" patients. *Id.* Apfel also suggests changing the anesthetic technique by

avoiding, for example, volatile anesthetics entirely and using only intravenous anesthesia. *Id.* Applicant notes that references 21 and 22 in Apfel (Appendices 3 and 4), upon which Apfel bases part of these conclusions, appear to merely mention or study the possible antiemetic properties of various anesthetic strategies, using *e.g.*, intravenous propofol with or without inhalation of nitrous oxide, or ondansetron. However, Apfel fails to teach or suggest the method of reducing post-surgical vomiting as recited by the present claims.

The Action cites the Apfel reference to "show that PONV (postoperative nausea and vomiting) has been known in the prior art to be associated with general anesthesia. Apfel further teaches [that] a prophylactic antiemetic strategy should be considered when a patient is known to be at risk of PONV." Action, page 5. Applicant notes that the Action's comment echoes language in the specification on page 2, lines 25-29, for example. If anything, Apfel thus emphasizes the importance of the problem solved by the present invention and the long-felt need for a prevention and treatment of post-surgical vomiting, as discussed in Applicant's previous response of November 15, 2006, the comments of which are incorporated herein. Such evidence of long-felt need "must be evaluated by Office personnel" in considering an obviousness rejection. Guidelines, at 57527; *see also id.* ("Objective evidence relevant to the issue of obviousness... sometimes referred to as 'secondary considerations,' may include... long-felt but unsolved needs.... The evidence may be included in the specification as filed...."). This long-felt need is also addressed by the specification's discussion of how oral administration allows patients to ingest at least part of the Doxylamine Succinate and Pyridoxine Hydrochloride before or after surgery, such as at home. *See* page 15, lines 5-6. This is to be contrasted with commonly used intravenous injections, which require the intervention of a qualified professional.

Moreover, nothing in Apfel teaches or suggests "(a) orally administering to the patient at least a first delayed release formulation comprising a therapeutically effective amount of

Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients the evening prior to surgery, and (b) orally administering to the patient a second delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients 0-6 hours after surgery." To the contrary, Applicant respectfully submits that traditional practice in the art of preventing post-surgical nausea and vomiting teaches away from orally administering a medication shortly after surgery. Indeed, the enclosed article entitled, "Managing Nausea and Vomiting" (Appendix 1) offers following statement: "[T]he restriction of oral intake until the return of bowel function after surgery has been used for decades to decrease the occurrence of postoperative nausea and vomiting." *See, e.g.*, page 42, last paragraph of central column. A reference that teaches away from the claimed invention is sufficient on its own to defeat a *prima facie* case of obviousness. *Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000).

iii. Ansel

Finally, Ansel merely teaches that delayed-release products usually are enteric coated tablets. Ansel, page 229, col. 1. This does not supplement for the deficiencies of the teachings by the above-mentioned references. Alone or in combination with Gervais and Apfel, there does not appear to be any teaching or suggestion with respect to this reference of Applicant's claimed features of "(a) orally administering to the patient at least a first delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients the evening prior to surgery, and (b) orally administering to the patient a second delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients 0-6 hours after surgery." Thus, this reference, alone or in combination, does not support the obviousness rejection.

c. Summary

The combination of cited references fails to teach or suggest all of the claimed features and do not render the claimed invention obvious. MPEP § 2143. In particular, the primary reference of Gervais, taken alone or in combination with Apfel and Ansel, does not teach or suggest every feature of independent claim 1, as amended.

In addition, Applicant has previously provided other detailed arguments and evidence of the existence of secondary considerations of non-obviousness (*e.g.*, surprising and unexpected results and satisfying long-felt need). *See* Applicant's response of November 15, 2006, which is incorporated herein by reference. Such secondary considerations confirm that the claimed invention is patentable over the cited references.

In view of all of these arguments, the obviousness rejection cannot stand. Applicant therefore respectfully requests that the rejection be withdrawn.

D. The Obviousness-Type Double Patenting Rejection Is Overcome

Claims 1-6, 13-18 and 19 are rejected for nonstatutory obviousness-type double patenting as being unpatentable over claims 25-29, and 30 of U.S. Application No. 09/885,051 to Gervais (U.S. Patent No. 6,340,695), which is the same reference used to support the obviousness rejections discussed above.

Applicant disagrees with the obviousness-type double patenting rejection. However, in an effort to further the prosecution and secure prompt allowance in this case, claim 1 has been amended to recite, "A method of reducing post-surgical vomiting in a patient 6-24 hours post-surgery comprising: (a) orally administering to the patient at least a first delayed release formulation comprising a therapeutically effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients the evening prior to surgery, and (b) orally administering to the patient a second delayed release formulation comprising a therapeutically

effective amount of Doxylamine Succinate and Pyridoxine Hydrochloride as active ingredients 0-6 hours after surgery", thus incorporating at least the subject matter of previous claim 8, which is not subject to the present rejection. The rejection is therefore overcome.

Should the rejection be nevertheless re-applied to present claim 1, Applicant submits that since this rejection is based on the same reference used to support each § 103(a) rejection, the arguments made above equally apply to this rejection and are therefore incorporated by reference. Applicant therefore requests that this rejection be withdrawn.

E. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-3015 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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